REMARKS

Restriction Requirement:

The restriction places an unfair burden on the applicant to prosecute and maintain separate applications on sequences, such as Pr33a and Pr33b, which are described in the above-identified application as structurally related transcripts, e.g., differing in Alu sequences. Given that these sequence share long stretches of sequence identity, it is clear that it would not be an undue burden to search for both. It is unclear why such a restriction between the two has been maintained.

Rejection under 35 U.S.C. §101:

A declaration by Dr. Zairen Sun has been provided which provides evidence that Pr33a is exquisitely and selectively expressed in prostate, and not in 23 other tissues surveyed. This data supports the statements made in the application (e.g., Page 3, lines 7-9; Page 3, lines 25-30) of tissue selectivity, as well as its utility as a tissue-specific marker. Tissue-specificity is an adequate showing of utility. See, e.g., *Revised Interim Utility Guidelines Training Materials*, Example 12. The example in the *Guidelines* is of a marker that is specific for a cancer – which is a type of tissue specificity. There is no reason why tissue specificity of normal tissue would not have analogous utility.

It is stated on Page 6 of the Office action that "its [Pr3a] selective expression in prostate as compared with the low levels of mRNA expression in other tissues also applies to many unrelated polynucleotides such as PSA ..." It is not clear why this is relevant. PSA is the recommended screening test for prostate cancer in men over 50. See, *Current Diagnosis*, Pages 14-15 (Exhibit 1). The utility of PSA is unrelated to its function, but necessarily depends on its tissue specificity. Prostate specific markers therefore have a recognized commercial utility. As

stated in the specification, because of its tissue specificity, Pr33 can be used as a marker in biopsies to detect the presence of prostate tissue, and also to detect metastatic cells. See, e.g., Specification, Page 26. The Patent Office has not provided any evidence or scientific reasoning to support the position that the utility disclosed herein does not meet the statutory requirements of 35 U.S.C. §101. The rejection is illogical, and counter to the policy reasons behind the establishment of the U.S. Patent system. Applicant's discovery of a polynucleotide specifically expressed in prostate is precisely the type of useful invention the Patent Office was created to reward.

The fact that other markers have been show to be prostate tissue-specific is not any ground to question the utility of the claimed sequence. For example, many drug targets have multiple ligands, where each ligand has the same receptor specificity, and each possesses substantial utility as evidenced by a commercial market replete with drugs that target the same receptor(s). The Patent Office's argument is not well-reasoned.

Rejection under 35 U.S.C. §112, first paragraph:

The claims have been amended to recite that the complements to the recited sequence are "100% identical thereto."

It is stated in the Office action on Page 17 that there is no written description of the phrases "1-5198" and "1763-5198." However, there is no requirement that the specification provide *ipsis verbis* description of the claims. This issue was faced in *In re Wertheim*, 191 USPQ 90, 98 (CCPA 1976). According to the *Wertheim* court:

> Claims 2, 37, and 38, which claim a solids content range of "between 35% and 60%," present a different question. They clearly claim a range within the described broad range of 25% to 60% solids; the question is whether, *on the facts,* the Patent and Trademark Office has presented sufficient reason to doubt that the broader described range also describes the somewhat narrower claimed range.

. . . . . .

> In the context of this invention, in light of the description of the invention as employing solids contents within the range of 25-60% along with specific embodiments of 36% and 50%, we are of the opinion that, as a factual matter, persons skilled in the art would consider processes employing a 35-60% solids content range to be part of Applicant's invention and would be led by the Swiss disclosure so to conclude. Cf. *In re Ruschig, supra*. The Patent and Trademark Office has done nothing more than to argue lack of literal support, which is not enough. If the lack of literal support alone were enough to support a rejection under §112, then the statement of *In re Lukach, supra* 58 CCPA at 1235, 442 F2d at 969, 169 USPQ at 796, that "the invention claimed does not have to be described in ipsis verbis in order to satisfy the description requirement of §112," is empty verbiage. The burden of showing that the claimed invention is not described in the specification rests on the Patent and Trademark Office in the first instance, and it is up to the Patent and Trademark Office to give reasons why a description is not in ipsis verbis is insufficient.

Similarly, the patent specification provides disclosure of a large number of sequence positions that fall within the 5217 nucleotides of SEQ ID NO: 1. See, e.g., Page 3, lines 12-15; Page 5, line 45-Page 6, line 21; Page 13, line 10-17. Clearly, applicant was in possession of not only the specific fragments of Pr33a identified in the application, but any intermediary fragments with its complete sequence. Under the same reasoning set forth in Wertheim, applicant should be entitled to claim the narrower range within the broader disclosed sequence.

In view of the above remarks, favorable reconsideration is courteously requested. If there are any remaining issues which could be expedited by a telephone conference, the Examiner is courteously invited to telephone counsel at the number indicated below.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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Attorney Docket No.: ORIGEN-0034

Date: February 13 2004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of

Zairen SUN

Serial No. : 09/996,956 Examiner: Susan Ungar, Ph.D

Filed : November 30, 2001 Group Art Unit: 1642

Title : PROSTATE POLYNUCLEOTIDES AND USES

DECLARATION

1. I, Zairen Sun, Ph.D., am an inventor of the subject matter described and claimed in the above-identified U.S. Patent Application (hereinafter, "the Application") which is assigned to OriGene Technologies.

2. It is stated in the Application that Pr33a is selectively expressed in the prostate. See, e.g., Application, Page 3, lines 7-9; Page 3, lines 25-30. This information was obtained from experiments, including the experiment described below, which was performed by me, or under my supervision.

3. Fig. 1 shows the expression pattern of Pr33a in human tissues in a twenty-four tissue panel. 1, brain; 2, heart 3, kidney; 4, spleen; 5, liver; 6, colon; 7, lung; 8, small intestine; 9, muscle; 10, stomach; 11, testis; 12, placenta; 13, salivary gland; 14, thyroid; 15, adrenal gland; 16, pancreas; 17, ovary; 18, uterus; 19, prostate; 20, skin; 21, PBL; 22, bone marrow; 23, fetal brain; 24, fetal liver. As clearly observed in the tissue panel, Pr33a is detected only in prostate tissues, but not in the other 23 tissues which were tested.

4. The results described in Fig. 1 were obtained according to the following procedures:

Polyadenylated mRNA was isolated from tissue samples, and used as a template

for first-strand cDNA synthesis. The resulting cDNA samples were normalized using beta-actin as a standard. For the normalization procedure, PCR was performed on aliquots of the first-strand cDNA using beta-actin specific primers. The PCR products were visualized on an ethidium bromide stained agarose gel to estimate the quantity of beta-actin cDNA present in each sample. Based on these estimates, each sample was diluted with buffer until each contained the same quantity of beta-actin cDNA per unit volume.

To detect gene expression, PCR was carried out on aliquots of the normalized tissue samples using gene-specific bases disclosed on Page 13 of the application,

PR33F (forward) TCATGAGGCATTTCAGAGTGC (SEQ ID NO 8)

PR33R (reverse) CCTCAGAAATCTCAGGGCTTGT (SEQ ID NO 10).

The reaction products were loaded on to an agarose (e.g., 1.5-2%) gel and separated electrophoretically. The lane at the far left of the panel contains molecular weight standards.

5. I declare further that all statements made in this Declaration are of my own knowledge and are true and that all statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

_____ _____

Zairen Sun Date

Table 1–8. Screening for cancer: American Cancer Society (1999) guidelines for the early detection of cancer in people without symptoms.[1]

Test or Procedure	Sex	Age	Frequency
Sigmoidoscopy, flexible, or— Colonoscopy, or— Air contrast barium enema	MF	50 and over[2]	Every 5 years Every 10 years Every 5–10 years
Stool test for occult blood	MF	50 and over[2]	Every year
Digital rectal examination	MF	50 and over[2]	Every year
Prostate examination[3]	M	50 and over[4]	At the time of each screening sigmoidoscopy, colonoscopy, or barium enema
Papanicolaou test	F	Women who are or have been sexually active or have reached age 18 years	Annually until at least three consecutive satisfactory normal annual examinations, then less often at discretion of physician
Pelvic examination	F	18–40	Every 1–3 years with Papanicolaou test. Not indicated if cervix has been removed for a nonmalignant condition.
		Over 40	Every year
Endometrial tissue sample	F	At menopause; women at high risk[5]	At menopause and thereafter at the discretion of the physician
Breast self-examination	F	20 and over	Every month
Breast physical examination	F	20–40 40 and over	Every 3 years Every year
Mammography	F	40 and over	Every year
Health counseling and cancer checkup[6]	MF	Over 20 Over 40	Every 3 years Every year
Chest x-ray	Not recommended		
Sputum cytologic examination	Not recommended		

[1]From Update January 1992: The American Cancer Society Guidelines for the Cancer-Related Check-Up. CA Cancer J Clin 1992;42:44; and from the American Cancer Society 1999 update.
[2]People should begin colorectal cancer screening earlier or undergo screening more often (or both) if they have any of the following colorectal cancer risk factors: (1) a personal history of colorectal cancer or adenomatous polyps; (2) a strong family history of colorectal cancer or polyps (cancer or polyps in a first degree relative younger than 60 or in two first-degree relatives of any age); (3) families with hereditary colorectal cancer syndromes (familial adenomatous polyposis and hereditary nonpolyposis colon cancer).
[3]Digital rectal examination and serum prostate-specific antigen; if either is abnormal, further evaluation by transrectal ultrasound and biopsy as indicated.
[4]For men with ≥ 10-year life expectancy. Screening is recommended for younger men if at higher risk (blacks, strong family history of prostate cancer).
[5]History of infertility, obesity, failure of ovulation, abnormal uterine bleeding, or unopposed estrogen or tamoxifen therapy.
[6]To include examination for cancers of the thyroid, testicles, ovaries, lymph nodes, oral region, and skin.

on the advisability of routine mammography for women aged 40–49, leaving the decision instead to the discretion of individual patients and their physicians. By contrast, based on recommendation from an expert advisory panel which cited evidence that breast cancers may grow more quickly in younger women, the American Cancer Society mammography screening guidelines were changed to include annual mammograms for women in their 40s.

Single serum PSA measurements appear to offer relatively high sensitivity and specificity to detect prostate cancer. The sensitivity is about 67%, the specificity about 82%, and the positive predictive value for prostate cancer is about 43%. When both the digital rectal examination and serum PSA are abnormal, PSA specificity increases, but sensitivity falls (to 33%), and predictive value rises only slightly (to 49%). Whether early detection and treatment alters the natural course of the disease remains to be seen. There are still no data on the morbidity and mortality benefits of such screening. Two randomized controlled trials are under way. Unlike the American College of Physicians, the American Cancer Society recommends annual PSA testing for men

over age 50. Screening is not recommended for men who have estimated life expectancies of less than 10 years. Many physicians remain ambivalent about recommending its routine use.

In two separate studies, the risk of death from colon cancer among patients undergoing at least one sigmoidoscopic examination was reduced by 60–80% compared with that among those not having sigmoidoscopy. A recent finding of a 33% reduction in mortality rate from colorectal carcinoma in persons undertaking annual fecal occult blood testing (FOBT) has been more controversial. The predictive value of a positive FOBT was only 2.2%, and 38% of all patients screened underwent at least one follow-up colonoscopy during the 13-year study.

Screening for vaginal cancer with a Papanicolaou smear is not indicated in women who have undergone hysterectomies for benign disease with removal of the cervix.

Screening for other cancers in normal asymptomatic or even high-risk segments of the population is not recommended because adequate screening tests are not available.

[National Cancer Institute: Physician's Data Query—Screening and Prevention Recommendations] http://cancernet.nci.nih.gov/clinpdq/screening_h.html

American College of Physicians: Screening for prostate cancer. Ann Intern Med 1997;126:480. [NLM Cit ID: 97208747] (Instead of routine screening, the ACP recommends that physicians describe the potential benefits and known harms of screening, diagnosis, and treatment, listen to the patient's concerns, and then individualize the decision to screen.)

American College of Physicians: Suggested technique for fecal occult blood testing and interpretation in colorectal cancer screening: Clinical guideline: Part 1. Ann Intern Med 1997;126:808. [NLM Cit ID: 97282922]

Coley CM et al: Early detection of prostate cancer: Part II: estimating the risks, benefits, and costs. Ann Intern Med 1997;126:468. [NLM Cit ID: 97208746] (Decision analysis suggested that one-time digital rectal examination and PSA measurement may increase average life expectancy by approximately 2 weeks at a reasonable marginal cost for men aged 50–69.)

Elmore JG et al: Ten-year risk of false positive screening mammograms and clinical breast examinations. N Engl J Med 1998;338:1089. [NLM Cit ID: 98196615] (Over a 10-year period, one-third of women screened had a false-positive abnormal test result.)

Gabriel H, Wilson TE, Helvie MA: Breast cancer in women 65–74 years old: Earlier detection by mammographic screening. AJR Am J Roentgenol 1997;168:23. [NLM Cit ID: 97131261] (Screening mammography revealed significantly smaller and earlier stage tumors in 65- to 74-year-old women.)

Hartmann LC et al: Efficacy of bilateral prophylactic mastectomy in women with a family history of breast cancer. N Engl J Med 1999;340:77. [NLM Cit ID: 99091091] (Prophylactic mastectomy was associated with a > 90% reduction in incidence of breast cancer in moderate and high risk women.)

Holmes MD et al: Association of dietary intake of fat and fatty acids with risk of breast cancer. JAMA 1999;281:914. [NLM Cit ID: 99176374] (No evidence that lower intake of total fat or specific types of fat was associated with a decreased risk of breast cancer.)

Hostetler RM, Mandel IG, Marshburn J: Prostate cancer screening. Med Clin North Am 1996;80:83. [NLM Cit ID: 96110850] (The effectiveness of prostate cancer treatment is still unproved. In addition, prostate cancer may actually be multiple entities with different natural histories, needing different treatments and, consequently, different screening strategies.)

Huang Z et al: Dual effects of weight and weight gain on breast cancer risk. JAMA 1997;278:1407. [NLM Cit ID: 98016075] (Avoiding weight gain may help prevent postmenopausal breast cancer, especially for women not receiving postmenopausal hormone replacement therapy.)

Kerlikowske K et al: Likelihood ratios for modern screening mammography: Risk of breast cancer based on age and mammographic interpretation. JAMA 1996;276:39. [NLM Cit ID: 96290398] (The sensitivity of first screening mammography increased with age, but specificity was similar for all ages. Based on the risk of breast cancer before mammography, which increases with age, the risk of breast cancer after mammography rose from 0.01 for ages 30–39 years to 0.05 for ages 50–59 years and to 0.07 for ages 70 years and older.)

Laya MB et al: Effect of estrogen replacement therapy on the specificity and sensitivity of screening mammography. J Natl Cancer Inst 1996;88:643. [NLM Cit ID: 96218816] (Current use of estrogen replacement therapy is associated with lower specificity and lower sensitivity of screening mammography. The adjusted mammographic specificities for never users, former users, and current users of estrogen replacement therapy were 86%, 86%, and 82%, respectively. The sensitivities for never users, former users, and current users were 94%, 94%, and 69%, respectively. Lower specificity could increase the cost of breast cancer screening, and lower sensitivity may decrease its effectiveness.)

Muller AD, Sonnenberg A: Prevention of colorectal cancer by flexible endoscopy and polypectomy: A case-control study of 32,702 veterans. Ann Intern Med 1995; 123:904. [NLM Cit ID: 96072645] (Evidence that endoscopic polypectomies may reduce the risk for colorectal cancer by 50% for periods lasting up to 6 years.)

Ransohoff DF, Lang CA: Screening for colorectal cancer with the fecal occult blood test: A background paper. Clinical guideline: Part II. Ann Intern Med 1997;126:811. [NLM Cit ID: 97282923] (Screening fecal occult blood tests are positive in 1–16% of cases depending on the age of the person being tested, whether the sample is rehydrated, and whether the test is used for initial screening or for rescreening. When persons who have positive test results are evaluated, colorectal cancer is found in about 2–17%. Early colorectal cancer [Dukes stage A or B] is found in about 2–14%.)

Read TE et al: Importance of adenomas 5 mm or less in diameter that are detected by sigmoidoscopy. N Engl J Med 1997;336:8. [NLM Cit ID: 97122456] (In asymptomatic, average-risk patients with a benign adenoma on screening sigmoidoscopy, neoplasms were found in the proximal colon in 29% of those with diminutive index polyps, 29% of those with small index polyps, and 57%